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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/902,651	NAKANE ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,11-16 and 49-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,11-13,15 and 49-53* is/are allowed.

6)☒ Claim(s) *2-7,14,16 and 54-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/898,560.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-7, 11-16, and 49-63 are pending in the application.

[2] Applicant's amendment to the claims, filed on 12/22/06, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's arguments filed on 12/22/06 in response to the Office action mailed on 8/22/06 are acknowledged. Applicant's arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[4] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Reissue Oath/Declaration Reminder

[5] Applicant is reminded of MPEP 1444.II, which states (in relevant part), "[a] supplemental oath/declaration need not be submitted with each amendment and additional correction. Rather, it is suggested that the reissue applicant wait until the case is in condition for allowance, and then submit a cumulative supplemental reissue oath/declaration pursuant to 37 CFR 1.175(b)(1). See MPEP § 1414.01 for a discussion of the required content of a supplemental reissue oath/declaration under 37 CFR 1.175(b)(1)."

Specification

[6] The amendment filed 3/18/05 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the amendment to replace "at the position in the N-terminal direction from D of the C-terminal of said aspartic acid-rich domain" with "one amino acid position downstream of D2" and to replace "amino acid residues located at the first position in the N-terminal direction from D of the C-terminal and D of said C-terminal" with "first amino acid downstream of D2 and the first amino acid upstream of D3". See particularly amendments to column 4, lines 15-34 and amendment to column 5, line 66 to column 6, line 16 at pp. 4-5 of the specification amendment filed on 3/18/05.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Objection

[7] The objection to claims 8 and 33 as being in an improper format is withdrawn in view of the cancellation of the claims.

Claim Rejections - 35 USC § 112, Second Paragraph

[8] Claims 3, 5-6, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 3 (claim 16 dependent therefrom) is unclear in limiting "the reaction product of the mutant prenyl diphosphate synthase" of claim 1 to farnesyl diphosphate (emphasis added). The recitation of "the" in the phrase "the reaction product" is interpreted as meaning the polypeptide of claim 1 has only a single reaction product. However, as shown in Figure 3 of the 5,935,832 patent, the polypeptide of claim 1 (which is limited to those of Figure 3) has at least two reaction products, *i.e.,* geranylgeranyl diphosphate and farnesyl diphosphate. Thus, while the mutant of claim 1 has a reaction product that is farnesyl diphosphate, it does not have a single reaction product that is farnesyl diphosphate. It is suggested that applicant clarify the meaning of the claim.

[b] Claims 5-6 (claim 16 dependent therefrom) are rejected as being confusing as requiring the polypeptide of claim 1 to be an archaea or an *S. acidocladarius* prenyl diphosphate synthase for reasons that follow. Claim 1 has been amended to limit the prenyl diphosphate synthase to SEQ ID NO:1 with specific mutations. Claims 5 and 6, which depend from claim 1, limit the prenyl diphosphate synthase to being an archaea or *S. acidocladarius* prenyl diphosphate synthase, respectively, which is interpreted as a prenyl diphosphate synthase that is endogenous to archaea or *S. acidocladarius.* However, according to the specification, SEQ ID NO:1 having the modifications as recited in claim 1 does not appear to be endogenous to the thermophilic archaea bacterium, *S. acidocladarius* (see, *e.g.,* column 6, lines 21-63 and column 12, Example 4 of the 5,935,832 patent). As such, it is unclear as to how the polypeptide of claim 1, which has modifications that do not appear to be present in an endogenous *S.*

acidocladarius prenyl diphosphate synthase, is simultaneously an archaea or *S. acidocladarius* prenyl diphosphate synthase. It is suggested that applicant clarify the meaning of the claims.

Claim Rejections - 35 USC § 112, First Paragraph

[9] The new matter rejection of claims 2 and 16 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record (paragraph 13 beginning at p. 6 of the prior Office action) and the reasons stated below. The rejection was fully explained in prior Office actions. New claims 54-63 are included in the instant rejection as reciting limitations that were held to be new matter in the prior Office action. Thus, claims 2, 16, and 54-63 are rejected.

RESPONSE TO ARGUMENT: Regarding the limitation of "synthesizes about as much or more prenyl diphosphate than the amount of prenyl diphosphate synthesized by the wild type prenyl diphosphate synthase under similar conditions" in claim 2 (claim 16 dependent therefrom), applicant argues (instant response at p. 16, paragraph 13) the rejection is obviated by amendment to claim 1.

Applicant's argument is not found persuasive. The amendment to claim 1 to limit the polypeptide of claim 1 to specific variants of SEQ ID NO:1 is acknowledged. However, as noted in the prior Office action, while the examiner can find support in the specification for the mutant of claim 1, "wherein said mutant...synthesizes farnesyl diphosphate which is shorter than prenyl diphosphate synthesized by a corresponding wild-type" (column 6, lines 17-20 of the '832 patent) or wherein the mutant synthesizes

a greater amount of farnesyl diphosphate than the wild-type as evidenced by Figure 3, the examiner can find no support in the original application for the limitation of "synthesizes about as much or more prenyl diphosphate than the amount of prenyl diphosphate synthesized by the wild type prenyl diphosphate synthase under similar conditions" in claim 2 (see p. 7, lines 9-11). The amendment to claim 1 fails to obviate the rejection because there is no express, implicit, or inherent support for the mutant polypeptide of claim 1, wherein the mutant "synthesizes about as much or more prenyl diphosphate than the amount of prenyl diphosphate synthesized by the wild type prenyl diphosphate synthase under similar conditions" as recited in claim 2.

Addressing the limitations of "wherein said mutant prenyl diphosphate synthase synthesizes a greater amount of a prenyl diphosphate of a first chain length than is synthesized by a corresponding wild-type...and wherein said wild-type prenyl diphosphate synthase may or may not synthesize said prenyl diphosphate of said first chain length" as recited in lines claims 54 (claims 55-57 dependent therefrom), 58 (claims 59-61 dependent therefrom), and 62-63, applicant argues the rejection is obviated by limiting the region of mutation in the mutant of claims 54, 58, 62, and 63.

Applicant's argument is not found persuasive. The amendment to claim 1 to limit the region of modification in the claimed mutant is acknowledged. However, as noted in the prior Office action, while the examiner can find support in the specification for the mutant of claim 1, "wherein said mutant...synthesizes farnesyl diphosphate which is shorter than prenyl diphosphate synthesized by a corresponding wild-type" (column 6, lines 17-20 of the '832 patent) or wherein the mutant synthesizes a greater amount of

farnesyl diphosphate than the wild-type as evidenced by Figure 3, the examiner can find no support in the original application for the limitations of "wherein said mutant prenyl diphosphate synthase synthesizes a greater amount of a prenyl diphosphate of a first chain length than is synthesized by a corresponding wild-type...and wherein said wild-type prenyl diphosphate synthase may or may not synthesize said prenyl diphosphate of said first chain length." The amendment to limit the region of modification fails to obviate the rejection because there is no express, implicit, or inherent support for the functional limitations of the claimed mutant as noted above.

Applicant is invited to show support for the limitation at issue.

[10] The new matter rejection of claim(s) 7 and 16 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record (see paragraph 15 beginning at p. 10 of the prior Office action) and the reasons stated below. The rejection was fully explained in prior Office actions.

RESPONSE TO ARGUMENT: Applicant argues (instant response at p. 16, paragraph 15) the rejection is obviated by amendment to claim 1.

Applicant's argument is not found persuasive. The amendment to claim 1 to limit the polypeptide of claim 1 to specific variants of SEQ ID NO:1 is acknowledged. As noted in the prior Office action, the disclosure for which applicant relies on as supporting the limitations of claim 7, "shows the effects...as a function of temperature over a defined temperature range" (emphasis original; p. 11, top). The specification discloses that the five mutant polypeptides as encompassed by claim 1 "show thermo resistance

almost equal to that owned by the native geranylgeranyl diphosphate synthase (column 7, lines 1-3). Thus, while the disclosure supports the mutant of claim 1 that has a thermostability that is "almost equal" to that of wild-type, the cited disclosure *does not* support a polypeptide as encompassed by claim 1 that is "at least as thermostable as...wild-type" (emphasis added), wherein the term "at least" has no definable upper limit. See *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976).

Applicant is invited to show support for the limitation at issue.

[11] Claims 54-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

MPEP § 2163.II.A.3.(b) states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description."

Claims 54 (claims 55-57 dependent therefrom) and 58 (claims 59-61 dependent therefrom) recite the limitation "wherein said sequence of said mutant prenyl diphosphate synthase is modified...only in the amino acid sequence beginning at the

position five amino acids upstream of said aspartic acid rich domain..." By recitation of "modified...only in the amino acid sequence beginning at the position five amino acids upstream of said aspartic acid rich domain," the examiner has interpreted the claim to include mutation at the amino acid five positions N-terminal to the aspartic acid rich domain. However, while the specification and claims support modification *between* D1 and the fifth position upstream of D1, the examiner can find no express, implicit, or inherent support in the original application for an amino acid modification *including* the fifth position upstream of D1 as encompassed by the above limitation.

Applicant is invited to show support for such limitations as noted above.

[12] Claims 58-61 and 63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

MPEP § 2163.II.A.3.(b) states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description."

Claims 58 (claims 59-61 dependent therefrom) and 63 recite the limitation "...said at least one amino acid substitution located at at least one amino acid position selected from...(b) the amino acid residue located one amino acid position downstream of D2; (2) at least one additional amino acid inserted between the first amino acid downstream of D2 and the first amino acid upstream of D3..." While the examiner can find support for the amino acid modification(s) of "at least one amino acid residue selected from (a) the amino acid residues in between the amino acid residue located at the fifth position in the N-terminal direction from D of the N-terminal and the amino acid residue located at the first position in the N-terminal direction from D of said N-terminal of the aspartic acid-rich domain DDXX(XX)D (wherein X denotes any amino acid, and the two X's in the parentheses may not be present) present in region II, and (b) the amino acid residue located at the first position in the N-terminal direction from D of the C-terminal of said aspartic acid-rich domain has been substituted by another amino acid, and/or (8) an additional one or more amino acids have been inserted in between the amino acid residue located at the first position in the N-terminal side from D of the C-terminal and D of said C-terminal of said aspartic acid-rich domain" (paragraph bridging columns 5 and 6), the examiner can find no express, implicit, or inherent support for the amino acid modifications as encompassed by the above limitations in the original application.

Applicant is invited to show support for such limitations as noted above.

[13] Claims 62-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

MPEP § 2163.II.A.3.(b) states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description."

Claims 62-63 recite the limitations, "[a] mutant prenyl diphosphate synthase...modified...only within region II...wherein region II of said amino acid sequence of said wild-type prenyl diphosphate synthase is 45% homologous with the sequence consisting of positions 72 through 93 of SEQ ID NO:1." According to applicant, support for claims 62-63 can be found "at column 4, line 60 through column 5, line 7; column 5, line 66, through column 6, line 21; column 6, lines 59 through 64; Example 2, in column 10; Example 4, in column 12; and, in Figure 1 (see p. 15 of the instant remarks). According to applicant, "[t]his definition of region II corresponds to the wild-type sequences disclosed in Figure 1 of the specification" (see p. 12 of the instant remarks, addressing support for claim 62).

It is acknowledged that Figure 1 appears to define Region II of "GGPS.pep." (disclosed as being *S. acidocaldarius* prenyl diphosphate synthase at column 4, line 60-67) as being the amino acid sequence VLHTFTLVHDDIMDQDNIRRG, which is amino acids 72-93 of SEQ ID NO:1. The examiner has carefully reviewed applicant's cited supporting disclosure. While the examiner can find support for modification of "at least one amino acid residue selected from (a) the amino acid residues in between the amino acid residue located at the fifth position in the N-terminal direction from D of the N-terminal and the amino acid residue located at the first position in the N-terminal direction from D of said N-terminal of the aspartic acid-rich domain DDXX(XX)D (wherein X denotes any amino acid, and the two X's in the parentheses may not be present) present in region II, and (b) the amino acid residue located at the first position in the N-terminal direction from D of the C-terminal of said aspartic acid-rich domain has been substituted by another amino acid, and/or (8) an additional one or more amino acids have been inserted in between the amino acid residue located at the first position in the N-terminal side from D of the C-terminal and D of said C-terminal of said aspartic acid-rich domain" (paragraph bridging columns 5 and 6), the examiner can find no express, implicit, or inherent support for any modification "within region II," wherein region II of the wild-type is "45% homologous" to the amino acid sequence of amino acids 72-93 of SEQ ID NO:1 as recited in claims 62-63. In this case, the original application would not appear to support the limitations of any modification within "region II," wherein "region II" is defined as an amino acid sequence that "is 45% homologous with the sequence consisting of positions 72 through 93 of SEQ ID NO:1."

Applicant is invited to show support for such limitations as noted above.

[14] The written description rejection of claim(s) 1, 3-4, and 15-16 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendment to claim 1 to limit the claimed mutant polypeptide to specific mutants of SEQ ID NO:1, *i.e.,* the T78F, H81A variant of SEQ ID NO:1; the T78F, H81L variant of SEQ ID NO:1; the F77Y, T78F, H81L variant of SEQ ID NO:1; the F77Y, T78F, H81A variant of SEQ ID NO:1; and the F77Y, T78S, V80I, I84L, 84PS85 variant of SEQ ID NO:1. See, *e.g.,* mutants of SEQ ID NO:1 in Figures 2 and 3.

[15] The written description rejection of claim(s) 2 and 5-7 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action. Newly added Claims 54-63 are included in the instant rejection. Thus, claims 2, 5-7, and 54-63 are rejected.

RESPONSE TO ARGUMENT: Applicant argues the claims have been amended to require modification only in the amino acid sequence beginning at the position five amino acids upstream of the aspartic acid rich domain and ending at position D3 (claims 54 and 58) or to require modification only within region II of the wild-type prenyl diphosphate synthase. According to applicant, the rejection is obviated by this amendment.

Applicant's argument is not found persuasive. Regarding claim 2, while it is acknowledged that the mutant of claim 1 is limited to SEQ ID NO:1 with the specifically

recited modifications and that these mutants would appear to synthesize a greater amount of farnesyl diphosphate as compared to SEQ ID NO:1 (see Figure 3 of the '832 patent), it is noted that there is no disclosure of the claimed mutant wherein the mutant has the activity of synthesizing about as much or more of any prenyl diphosphate as compared to that of the wild-type. As such, one of skill in the art would recognize that, while applicant was in possession of a mutant of claim 1 that synthesizes more farnesyl diphosphate as compared to SEQ ID NO:1, applicant was not in possession of the mutant of claim 1 that has the activity to synthesize about as much or more of any prenyl diphosphate as compared to that of the wild-type.

Regarding claims 5-6, according to the specification, SEQ ID NO:1 is the prenyl diphosphate synthase of "*Sulfolobus acidocaldarius*" (see, *e.g.*, column 6, lines 21-63 and column 12, Example 4 of the 5,935,832 patent). It is noted that the mutant of claim 1 was generated by altering the nucleic acid sequence encoding SEQ ID NO:1 (see particularly column 12, Example 4). As such, a skilled artisan would recognize that the mutant of claim 1 is not "an archaea" or a "*Sulfolobus acidocaldarius*" prenyl diphosphate synthase, but is a *mutant* form of "an archaea" or a "*Sulfolobus acidocaldarius*" prenyl diphosphate synthase. As such, one of skill in the art would recognize that, while applicant was in possession of the mutant of claim 1, applicant was not in possession of the mutant of claim 1 that is "an archaea" or a "*Sulfolobus acidocaldarius*" prenyl diphosphate synthase.

Regarding claim 7, according to the specification (column 13, lines 15-17), "[t]he mutant prenyl diphosphate synthase has exhibited a thermo stability which is equal to

that of the native geranylgeranyl diphosphate synthase" as evidenced by Figure 2. As such, one of skill in the art would recognize that, while applicant was in possession of the mutant of claim 1 with "a thermo stability that is equal" to wild-type, applicant was not in possession of the mutant of claim 1 that has an unlimited increase in thermostability as encompassed by claim 7.

Regarding claims 54-63, applicant's amendment to limit the area of modification is acknowledged. However, this amendment fails to obviate the written description rejection. The claims are drawn to a genus of mutant prenyl diphosphate synthase polypeptides, wherein the amino acid sequence of the mutant – except for having an aspartic acid rich domain – is essentially unlimited. While applicant may argue that the sequence of the mutant outside of the recited area of mutation is that of a "wild-type," it is noted that the genus encompasses any wild-type sequence from any source, including those "wild-type" prenyl diphosphate synthase enzymes that have been isolated after the time of the invention. Further, the mutant has the function of synthesizing a greater amount of any prenyl diphosphate synthase with a shorter chain length as compared to the wild-type. As such, even in view of the amendment, the claims encompass widely variant species of mutant prenyl diphosphate synthase polypeptides. The specification discloses only five representative species of such mutants, which are all variants of the aspartic acid rich domain of SEQ ID NO:1. At the time of the invention, the prior art acknowledged a high level of unpredictability in altering the amino acid sequence of a polypeptide and the resulting effect(s) on its function. See particularly the teachings of Branden et al., Witkowski et al., and Ohnuma

et al. at pp. 17-18 of the Office action mailed on 9/29/04. As such, it is the examiner's position that the five variants of SEQ ID NO:1 fail to reflect the wide variation in structure and function as encompassed by the genus of claimed mutant prenyl diphosphate synthase polypeptides.

Given the lack of description of a representative number of polynucleotides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[16] The scope of enablement rejection of claim(s) 1, 3-4, and 15-16 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendment to claim 1 to limit the claimed mutant polypeptide to specific mutants of SEQ ID NO:1, *i.e.,* the T78F, H81A variant of SEQ ID NO:1; the T78F, H81L variant of SEQ ID NO:1; the F77Y, T78F, H81L variant of SEQ ID NO:1; the F77Y, T78F, H81A variant of SEQ ID NO:1; and the F77Y, T78S, V80I, I84L, 84PS85 variant of SEQ ID NO:1. See, *e.g.,* mutants of SEQ ID NO:1 in Figures 2 and 3.

[17] The scope of enablement rejection of claim(s) 2, 5-7, and 14 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action. The rejection was fully explained in a prior Office action. Newly added Claims 54-63 are included in the instant rejection. Thus, claims 2, 5-7, 14, and 54-63 are rejected.

RESPONSE TO ARGUMENT: Applicant argues the claims have been amended to require modification only in the amino acid sequence beginning at the position five amino acids upstream of the aspartic acid rich domain and ending at position D3 (claims 54 and 58) or to require modification only within region II of the wild-type prenyl diphosphate synthase. According to applicant, the rejection is obviated by this amendment.

Applicant's argument is not found persuasive. Regarding claim 2, while it is acknowledged that the mutant of claim 1 is limited to SEQ ID NO:1 with the specifically recited modifications and that these mutants would appear to synthesize a greater amount of farnesyl diphosphate as compared to SEQ ID NO:1 (see Figure 3 of the '832 patent), it is noted that the specification fails to provide the necessary guidance for making the mutant of claim 1 with the activity of synthesizing about as much or more of any prenyl diphosphate as compared to that of the wild-type as broadly encompassed by the claim and one of skill in the art would have no expectation of achieving such a result from the claimed mutant. It is the examiner's position that without such guidance, undue experimentation is required to make the mutant of claim 2.

Regarding claims 5-6, according to the specification, SEQ ID NO:1 is the prenyl diphosphate synthase of "*Sulfolobus acidocaldarius*" (see, *e.g.,* column 6, lines 21-63 and column 12, Example 4 of the 5,935,832 patent). It is noted that the mutant of claim 1 was generated by altering the nucleic acid sequence encoding SEQ ID NO:1 (see particularly column 12, Example 4). As such, a skilled artisan would recognize that the mutant of claim 1 is not "an archaea" or a "*Sulfolobus acidocaldarius*" prenyl

diphosphate synthase, but is a *mutant* form of "an archaea" or a "*Sulfolobus acidocaldarius*" prenyl diphosphate synthase. The specification fails to provide guidance for making "an archaea" or a "*Sulfolobus acidocaldarius*" prenyl diphosphate synthase that is simultaneously a mutant thereof. It is the examiner's position that without such guidance, undue experimentation is required to make the mutant of claims 5-6.

Regarding claim 7, the breadth of the claim encompasses the mutant of claim 1, wherein the mutant has an unlimited thermostability as compared to wild-type. However, according to the specification (column 13, lines 15-17), "[t]he mutant prenyl diphosphate synthase has exhibited a thermo stability which is equal to that of the native geranylgeranyl diphosphate synthase" as evidenced by Figure 2. In this case, the specification fails to teach a skilled artisan how to make the mutant of claim 7 with an unlimited thermostability as compared to wild-type. It is the examiner's position that without such guidance, undue experimentation is required to make the mutant of claims 5-6.

Regarding claim 14, while the specification is enabling for an isolated host organism, the specification fails to enable any host organism encompassed by the claim, which, according to the specification, encompasses a plant (column 7, lines 44-45). As noted in a prior Office action, even as late as 2002, the art recognizes a high level of unpredictability in making a transgenic plant (see Vain et al. *Theor Appl Genet* 105:878-889, particularly p. 878, right column, top), the teachings of which appear to be undisputed by applicant. The specification fails to provide guidance for making a transgenic plant as encompassed by the claims and in view of the lack of guidance and

the high level of unpredictability, it is the examiner's position that undue experimentation is required to make the full scope of the claimed invention.

Regarding claims 54-63, applicant's amendment to limit the area of modification is acknowledged. However, this amendment fails to obviate the scope of enablement rejection. The claims broadly encompass all mutant prenyl diphosphate synthase polypeptides, wherein the amino acid sequence of the mutant – except for having an aspartic acid rich domain – is essentially unlimited. Further, the mutant has the function of synthesizing a greater amount of any prenyl diphosphate synthase with a shorter chain length as compared to the wild-type. The specification discloses only five working examples of the scope of claimed mutant prenyl diphosphate synthase polypeptides, *i.e.,* the T78F, H81A variant of SEQ ID NO:1; the T78F, H81L variant of SEQ ID NO:1; the F77Y, T78F, H81L variant of SEQ ID NO:1; the F77Y, T78F, H81A variant of SEQ ID NO:1; and the F77Y, T78S, V80I, I84L, 84PS85 variant of SEQ ID NO:1. There is no disclosure or guidance for making such mutations within other prenyl diphosphate synthase polypeptides with an expectation of achieving the recited functions. Further, as noted in prior Office actions, there was a high level of unpredictability in altering the sequence of a protein as evidenced by the references of Branden et al., Witkowski et al., and Ohnuma et al. at pp. 17-18 of the Office action mailed on 9/29/04. See particularly the teachings of Ohnuma et al., which teach that mutation results in a prenyl diphosphate product with *longer* chain length relative to wild-type. While methods of altering the sequence of a polypeptide were known at the time of the invention, it was not routine to screen for all mutant polypeptides as broadly encompassed by the claims.

In view of the broad scope of the claims, the lack of guidance and working examples, the high level of unpredictability as supported by the prior art, and the significant amount of trial and error experimentation required, which was not typically practiced at the time of the invention, the specification fails to enable the full scope of the claimed invention without undue experimentation.

Double Patenting Rejection(s)

[18] The obviousness-type double patenting rejection of claims 1-6 and 8-10 as being unpatentable over claims 1 and 4 of US Patent 5,807,725 is withdrawn and the obviousness-type double patenting rejection of claims 11 and 13-15 as being unpatentable over claims 1-4 of US Patent 5,882,909 is withdrawn. The claims implicitly (claims 1-7) or explicitly (claims 54-63) require the mutant enzyme to synthesize prenyl diphosphate that is *shorter* as compared to wild-type. In contrast, the claimed *S. acidocaldarius* geranylgeranyl phosphate synthase mutants of the '725 patent and the '909 patent are disclosed as synthesizing prenyl diphosphate with a *longer* chain length relative to wild-type.

Conclusion

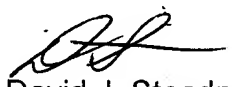
[19] Status of the claims:

- Claims 1-7, 11-16, and 49-63 are pending.
- Claims 2-7, 14, 16, and 54-63 are rejected.
- Claims 1, 11-13, 15, and 49-53 appear to be free of the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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